The Pharmacology of Amanita Muscaria

PETER G. WASER
Department of Pharmacology, University of Zurich, Zurich, Switzerland

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Introduction

Rarely, to-day, are new natural products with an interesting pharmacological action found in Swiss plants. Most alkaloids have been discovered and extensively investigated in the past 50 years. For us remains the search for new active compounds (alkaloids, amines and aminoacids etc.), which are present only in small concentrations, or which show interesting biological properties not yet investigated.

The starting point most often is the centuries-old knowledge of remarkable and unusual actions of a plant or its crude drug form, on man after ingestion. Intoxication after an overdose is the overall response of the organism to the toxic principles in the plant. This reaction is a sum of very different pharmacological actions, and may be very complicated. As plants vary in metabolism and production of active principles corresponding to their environment, comparison of intoxication symptoms will show regional differences. Different varieties of the same species may produce quite different metabolites.

The pharmacologist first has the problem of carefully scrutinizing the symptoms of intoxication, or, if these are already known, the therapeutic use by primitive tribes. He then must try to classify these symptoms as pharmacological actions on different organ systems, following the large knowledge of typical drug-actions. Then he develops a method for screening the active principles to isolate and concentrate these from the extracts, with the help of specific tests. For this part, cooperation with an interested chemist is the most important mutual help. Both have to adjust their extrac-

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tion and screening methods in order to isolate the active compounds. Very often the pharmacologist works with several independent tests, or a test battery which allows him to differentiate between several active principles. Finally, he has the rewarding task of investigating the actions of new and pure compounds of a plant, which so far were known only in primitive medicine.

The investigation of the pharmacology of amanita muscaria is a typical example of this procedure. It gave us the opportunity to investigate for the first time muscarine in its pure form. Now, the psychoactive principles are getting more of our interest. Already important facts are known and new active principles are discovered, but we feel that more must be found to explain the different astonishing effects of the fly agaric on man. My report therefore is not a final explanation and scientific description of active compounds, but more an account of our present knowledge and experiments under way. Finally, I want to describe our mode of detecting new hallucinogenic principles.

Muscarine

General

Because of its potent pharmacological actions muscarine, the best known alkaloid of amanita muscaria, has been studied by pharmacologists for over 100 years. It was the first drug with a selective action on organs innervated by the autonomic nervous system. The findings of these investigations, however, were uncertain and inaccurate until the isolation and crystallization of muscarine chloride from amanita muscaria (Eugster and Waser, 1954) (Table 1). The first preparations contained large amounts of choline, which is biologically less active, and unstable acetylcholine, which may be found in different mushrooms. These contaminations made standardization inaccurate.

All screening methods used for isolation of muscarine are based on its strong parasympathomimetic activity. Until to-day, muscarinic activity is the most used term for direct peripheral action on cholinergic receptors, situated in different smooth muscles, especially of the gastrointestinal tract and eye, exocrine glands and heart. Nicotinic action is reserved for cholinergic receptors in ganglionic synapses and endplates of skeletal muscle, where nicotine is stimulatant and depressant, and where muscarine has only small or no action. Lately, even in the central nervous system these types of muscarinic (cortical neurons, Betz cells), nicotinic (Renshaw cells) and intermediate synapses (thalamic neurons, caudate nucleus), have been demonstrated (McLennan, 1965). Without doubt acetylcholine plays a major role as a chemical neuro-transmittor in the brain.

Screening methods for muscarine

As other investigators (Kögl, Duisberg and Erxleben, 1931) before us, we used the isolated frog heart of Straub, which is very sensitive, (0.003–0.01μg muscarine-chloride) for small amounts of cholinergic drugs, their action be-

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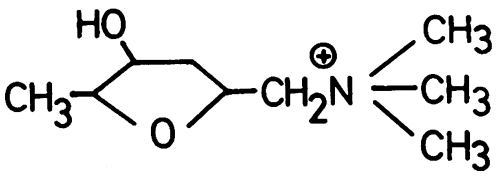
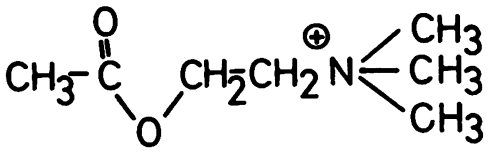
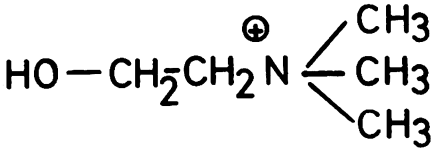
TABLE 1.—*Compounds isolated from Amanita muscaria (1966)*



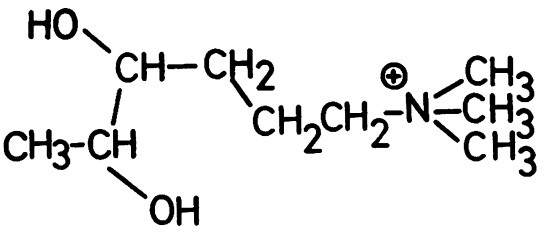
Muscarine
0,0002 %



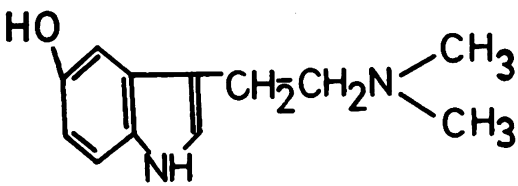
Acetylcholine



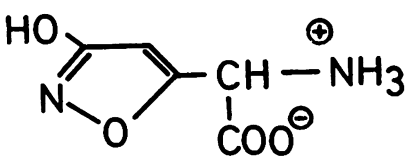
Choline



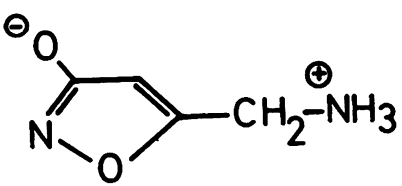
Muscaridine ?



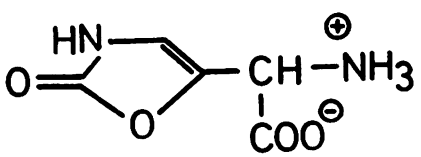
Bufotenine ?



Ibotenic acid
0,03 – 0,1 %



Muscimol



Muscazon

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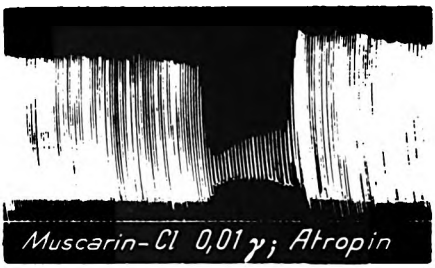

FIG. 1a.—Isolated frog heart (Straub). Muscarine diminishes amplitude of contraction and slows heart rate. Atropine (10^{-6} m) is an immediate antagonist.

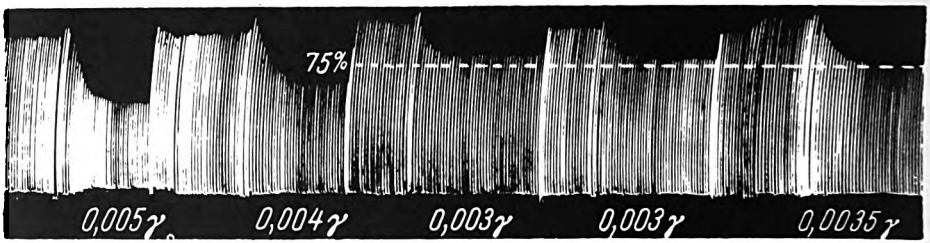

FIG. 1b.—Quantitative determination of muscarine with isolated frog heart. 25% paralysis is produced by 0.0035 μg muscarine-chloride.

ing immediately antagonised by atropine (Fig. 1). Concentration of muscarine from extracts by chromatography was followed until the final crystallization of pure muscarine-chloride. Biological methods are indispensable for the first isolation of the active principle, but later more specific coloration methods of the paper chromatograms were used.

Less suited for screening purposes are miosis and salivation of mice after intraperitoneal injection of 60–130 μg/kg, and chromodacryorrhoea produced in rats by subcutaneous or intraperitoneal injection of 20–35 μg/kg muscarine-chloride. The diameter of mouse-pupils is normally 0.3–0.4 mm wide, and must be measured with a magnifying device (low power microscope) (Pulewka, 1932). Mydriatic opening of the pupil is much easier to measure than miotic contraction. Furthermore, quantitative determination of salivation, lacrimation or chromodacryorrhoea is quite difficult. It may be accomplished by sucking these fluids from mouth or eye on filter paper and measuring the wet or coloured area (Malone and Robichaud et al., 1961).

Effects on the animal

In addition to the secretory and miotic action on larger animals (rabbit, cat, dog, monkey), a variety of other effects may be seen (Waser, 1961). The cardiovascular system is very sensitive to muscarine. Blood pressure is lowered rapidly by small intravenous doses, (cat: 0.002–1.0 μg/kg) and heart rate is slowed. Cardiac arrest may occur when the action of muscarine is not antagonized by atropine (Fig. 2). Vagotomy does not influence the only

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peripheral action of muscarine. Respiratory effects are noted with small doses: increase in volume and rate of respiration (0.02–1.0 μg/kg i.v.), probably due to stimulation of the chemoreceptors of the carotid body, is followed by bronchoconstriction and obstruction of the respiratory pathways by profuse secretion of mucus. Again all these effects are antagonized by atropine.

Transmission through ganglionic synapses (superior cervical ganglion) is not changed with high intravenous doses (500 μg/kg) of muscarine, and no neuromuscular block develops in atropinized cats. But with isolated and perfused ganglion preparations, higher concentrations of muscarine evoke postganglionic response, especially when the ganglion has been chronically denervated (Konzett and Waser, 1956).

Effects on isolated organs

The intense action of muscarine on the isolated frog heart has already been mentioned. Most investigations were done on smooth muscle organs for the purpose of comparing its potency with that of acetylcholine. The preparation best suited is the ileum of the guinea pig. Acetylcholine makes an immediate contraction during 15–30 minutes and later spontaneous relaxation

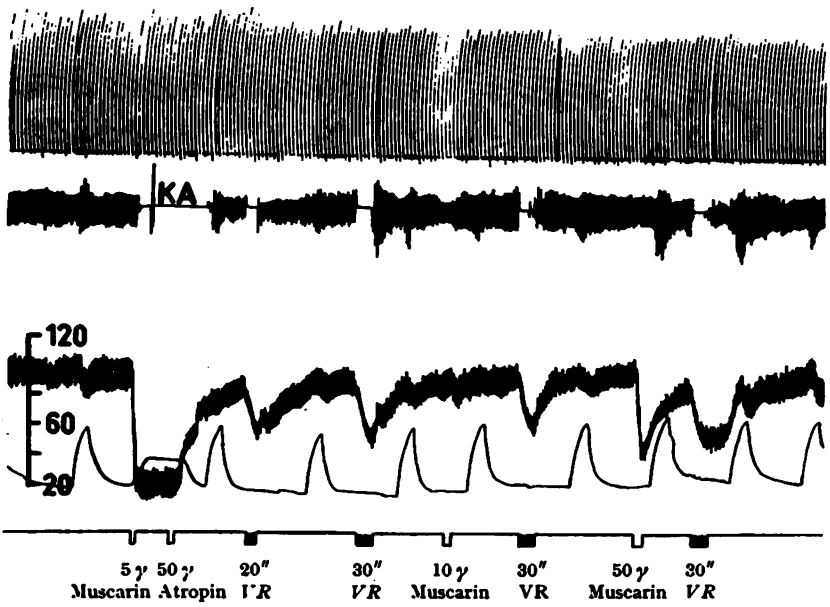

FIG. 2.—Cat in dial-nembutal narcosis. Registered are from top: twitches of m. gastrocnemius stimulated from n.ischiadicus tracheal respiration, blood-pressure in a.carotis, contractions of nictitating membrane stimulated from preganglionic sympathetic nerve. Signal: injected doses and denation of vagal stimulation (VR). Muscarine has no action on endplates in skeletal muscle, stops respiration by bronchoconstriction (KA=artificial respiration), lowers blood pressure and contracts nictitating membrane directly, atropine acts as antagonist.

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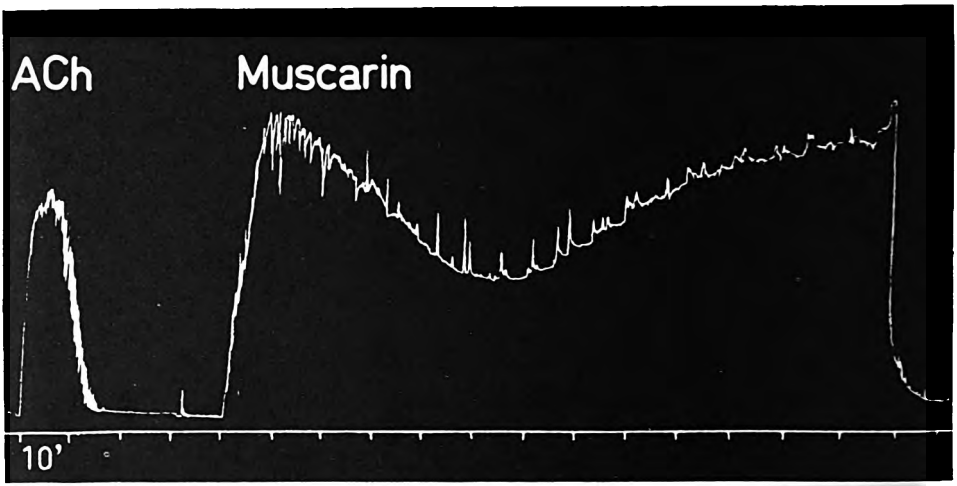

FIG. 3.—Guinea pig ileum. Contraction by acetylcholine (5×10^{-8} m Ach) and muscarine (3×10^{-8} m). Washing after 125 minutes. Slow and persistent contraction by muscarine with little twitches.

of the smooth muscle, by hydrolytic destruction of the molecule by tissue cholinesterases (Fig. 3). Muscarine shows a biphasic action. A rather quick but interrupted contraction is followed within 30 seconds by a slow phase of maximal contraction during 5–10 minutes. The relaxation after washing is at least two times slower than that after acetylcholine. Muscarine is not destroyed by cholinesterases; accordingly its action persists until the drug is removed by washing. Other contractions and twitches may follow.

Similar effects of muscarine on smooth muscle of other organs are found in many different species of animals. The average potency of contraction is much greater than with acetylcholine (Table 2). The isolated sphincter of the iris of pigs contracts with 10 times smaller concentrations of muscarine (10^{-7}m) than with acetylcholine (3.5×10^{-6}m). This explains well the miotic action on the intact animal (Fig. 4). Even high concentrations of muscarine (500 μg/ml) are not able to induce contraction of rectus muscle of the frog, and on nerve-muscle preparations no neuro-muscular block develops, as with curare.

TABLE 2.—*Spasmogenic activity of muscarine in isolated muscles. Average values from different animal species, activity ratio of muscarine to acetylcholine (=1)*

Tracheal chain	(guinea pig, rabbit)	150
Bladder wall (longitudinal and circular)	(guinea pig, rabbit, dog, rat, frog, horse, monkey)	46
Ureter	(horse)	29
Intestine (longitudinal and circular of duodenum, ileum, colon)	(frog, mouse, guinea pig, rabbit, dog, cat, horse, monkey)	8, 4
Uterus (longitudinal and circular)	(mouse, guinea pig, rat, horse, dog, rabbit)	4, 5

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Central nervous effects of muscarine

Until to-day nobody has been able to show a direct psychotropic action of muscarine on animal or man. This is probably due to its difficulty as a quaternary amine in passing the blood-brain barrier. Passage may be possible in combination with an amino acid or lecithin. The low oral toxicity of *d*,1-muscarine on mice (200 mg/kg), compared to its intravenous action (0.8 mg/kg), shows that resorption through the intestinal wall probably by a transport system, as with other depolarizing agents, is slow (Lüthi and Waser, 1965 and 1967). An interesting experiment on the monkey showed muscarine to have little effect orally (Fraser, 1957). No effect followed oral administration of 2 mg, despite the fact that the amount given was many times that which causes poisoning by the ingestion of amanita muscaria in the human being.

Gyermek and Unna (1960) attempted to eliminate the peripheral actions of muscarine by blocking the cholinergic receptors with atropine-methylbromide 15–20 minutes before the administration of muscarine. By this procedure the intravenous minimal lethal dose of *d*,1-muscarine was elevated from 1 mg/kg to over 160 mg/kg, but no central effects were recorded.

The electrophoretical local administration of acetylcholine, *d*,1-muscarine and other cholinomimetics has shown quite different neurones of the central nervous system (pyramidal cells of the cortex, cerebellar and thalamic neurons and Renshaw cells) to possess excitable muscarinic and nicotinic receptors (Curtis et al., 1961, 1964, 1966) (Krnjevic and Phillis, 1963). Cortical cells are extremely sensitive to acetylcholine, muscarone, muscarine and acetyl-β-methylcholine. There may be many other neurons which behave in a similar way, and we have to conclude that muscarine entering the brain will have different central and psychotropic actions. Although *choline* is well absorbed through the intestinal wall, most of it is rapidly metabolised and esterified in the tissue. Generally the action of free choline is similar to

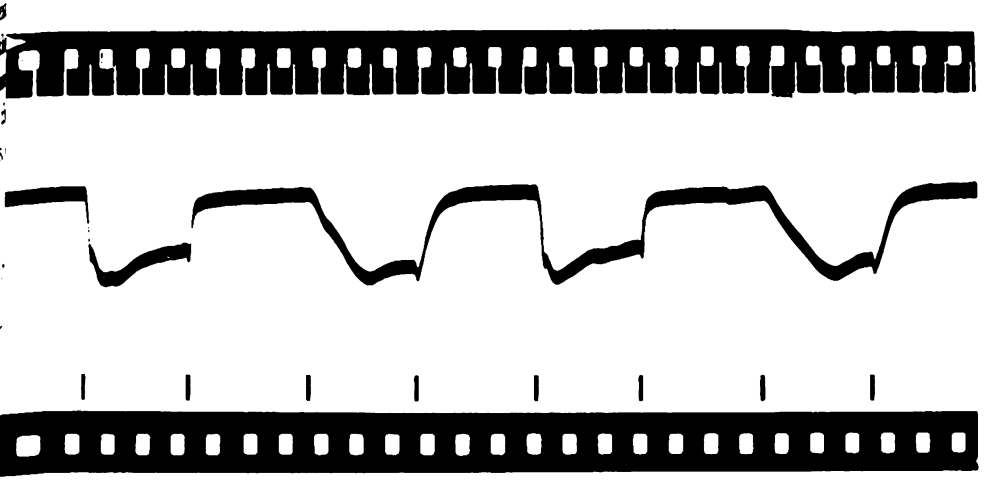

FIG. 4.—Contractions of m.sphincter iridis of pig by acetylcholine ($1:3{,}5\times10^{-6}$ m) and muscarine ($2:10^{-7}$ m). Time in minutes. Slow, gradual contraction by muscarine.

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acetylcholine, but the dose needed in different experiments is 200–100,000 times higher (Bovet, 1948). Direct electrophoretical application of choline to different neurons in the brain has no effect.

Centrally Acting Compounds

Atropine and tryptophane derivatives

As we have seen, the oral ingestion of muscarine cannot be responsible for the colourful amanita-intoxication of asian people described by travellers touring Siberia. Different explanations were given and additional central active ingredients were proposed. The unknown active principle was unfortunately given the name *Pilzatropin* or *muscaridine* by Kobert in 1891. The search for an atropine-like alkaloid in amanita muscaria has continued since then. Lewis (1955), reported the isolation of hyoscyamine from amanita muscaria and amanita pantherina in South Africa. Later, Polish chemists made a similar statement concerning their local mushrooms. Regardless of the very small concentration found in the mushrooms (<0.0001%), the symptoms of the intoxication do not fit the central effect of 10–30 mg of orally ingested atropine or belladonna-alkaloids, as scopolamine. Profuse salivation and perspiration, nausea, vomiting, bradycardy, mydriasis, are found, together with central excitation and delirious intoxication. Even small doses of atropine with hallucinations would immediately block the peripheral actions of muscarine (salivation, perspiration etc.). It would be prejudicial to treat here the pharmacology of atropine and similar bases before the presence of these alkaloids in the mushroom is demonstrated with certainty by chemical methods. Until now this evidence has not been substantiated or repeated by other research groups.

Another dubious proposal as a psychotropic principle in amanita muscaria is *bufotenine* (Table 1). This amine was isolated in considerable quantities from Amanita mappa, and detected in small amounts by paper chromatography in Amanita muscaria and Amanita pantherina (Wieland et al., 1953). When injected intravenously, bufotenine may have some hallucinogenic activity in man. This is denied by other research groups using oral administration of 50 mg bufotenine and intravenous injections of 20 mg. Eugster and Müller (1961) were not able to find bufotenine in Amanita muscaria.

Finally another quaternary amine, "*muscaridine*", (Table 1) was found in Amanita muscaria (Kögl, Salemink and Schuller, 1960) but chemical data on it are scarce and no pharmacological investigations were made.

Ibotenic acid, muscimol and muscazon

Lately, Eugster and co-workers have isolated and identified different new active substances from amanita muscaria which may—at least partly—explain its psychotropic action. The pharmacological screening of the isola-

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tion process was developed by W. Theobald.[1] It is based on the potentiating effect of these compounds on the narcosis produced by a short acting hypnotic (2-methoxy-4-allyl-phenoxyaceticacid-diethylamide), (Müller and Eugster, 1965; Good, Müller and Eugster, 1965). The narcosis potentiating principle of the mushroom consists of three different compounds (table 1). Sedative action of *muscazon* was much less than with *ibotenic acid* and *muscimol*. These two have a very pronounced hypnotic effect, and it is very probable that they also are psycho-active, although nothing definite has been described.

In order to demonstrate this sedative/hypnotic effect, we have injected mice with different doses intraperitoneally, and put them together with controls in activity cages (Fig. 5, 6). Sedative action is evident with 4–8 mg/kg ibotenic acid and 1–2 mg/kg muscimol. Oral administration is approximately half as effective as intraperitoneal injection.

These new compounds are rather toxic for mice. Muscimol is roughly 5–10 times more potent than ibotenic acid. Rats seem to be less sensitive (Table 3).

Table 3

		i.p.	p.o.
Toxicity in mice (LD 50)	Ibotenic acid	25 mg/kg	50 mg/kg
	Muscimol	6 mg/kg	12 mg/kg

Typical signs of intoxication develop similarly from both substances: nervousness, excitation, wide open eyes and dilated pupils, convulsions, twitches, tonic cramps, typical signs of catalepsy, irregular often accelerated respiration, later sedation and sleep.

Screening Methods for Hallucinogenic Drugs

In order to search for new active principles, we have to use other screening methods, which should be especially useful for finding compounds with psychotonic activity. The symptoms of intoxication most often show pharmacological effects resulting from the stimulation of central sympathetic structures. We find three methods to be of value for a general screening of numerous fractions of extracts with mice.

The most simple may be to measure the diameter of the mouse pupil during the toxicological assay. We use groups of ten mice per dose. Most hallucinogens, as LSD, Psilocybin, produce a marked dilatation. When the starting diameter with a standardized light source is small, this effect may be measured with ease. Of the new compounds, muscimol is especially effective (Fig. 7). The best way of application is intraperitoneal injection, but for comparision with the intoxication symptoms with the mushroom, oral ingestion may be preferred (Fig 8). Direct application of muscimol (0.5%) on the eye has no dilatory effect.

[1] Dr. W. Theobald, J. R. Geigy, A. G. Basel.

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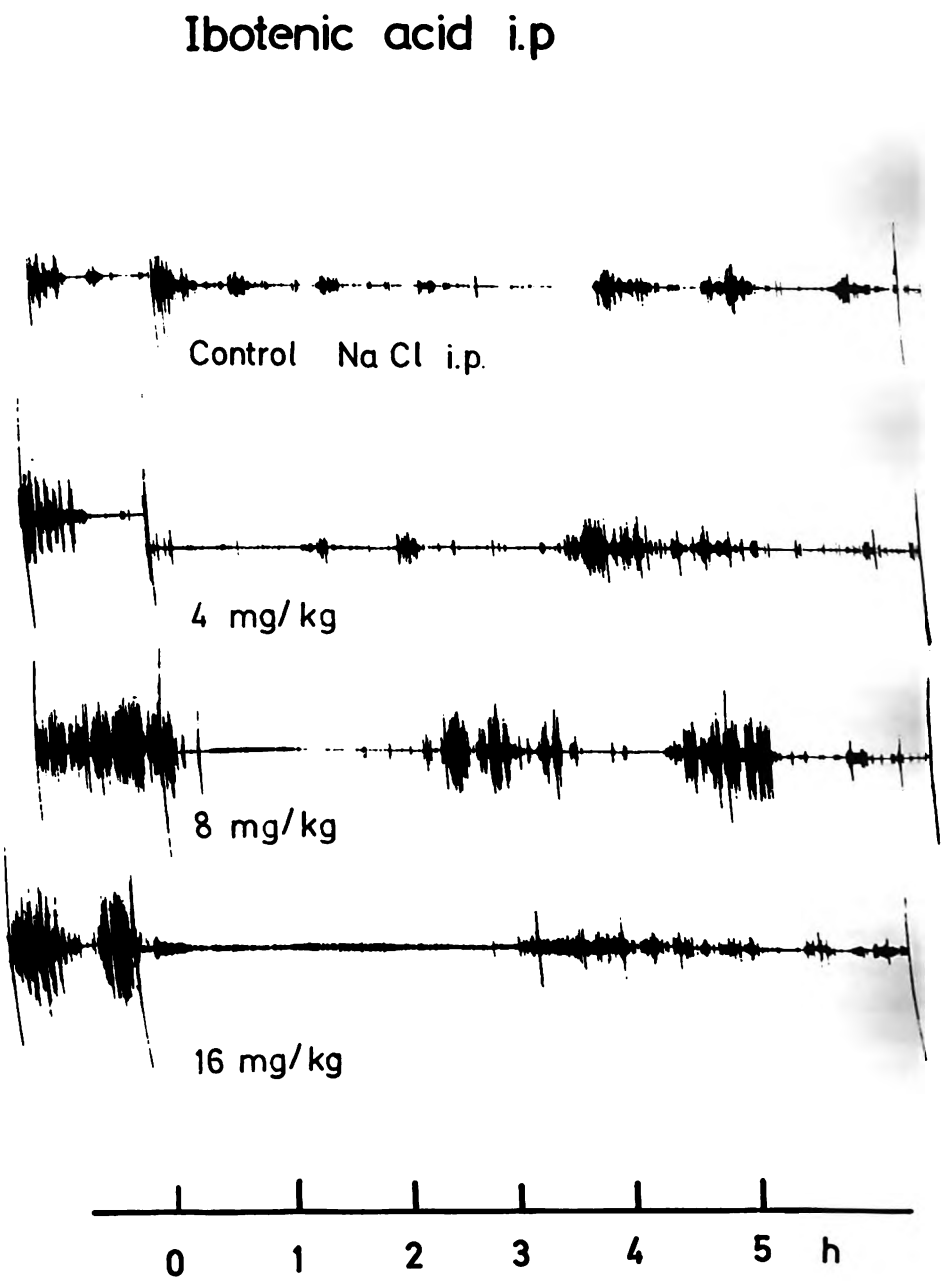

FIG. 5.—Mice in jiggle cage, intraperitoneal injection of ibotenic acid. 8 and 16 mg/kg produce sedation of 2 and 3 hours. In the first phase muscle twitching was recorded.

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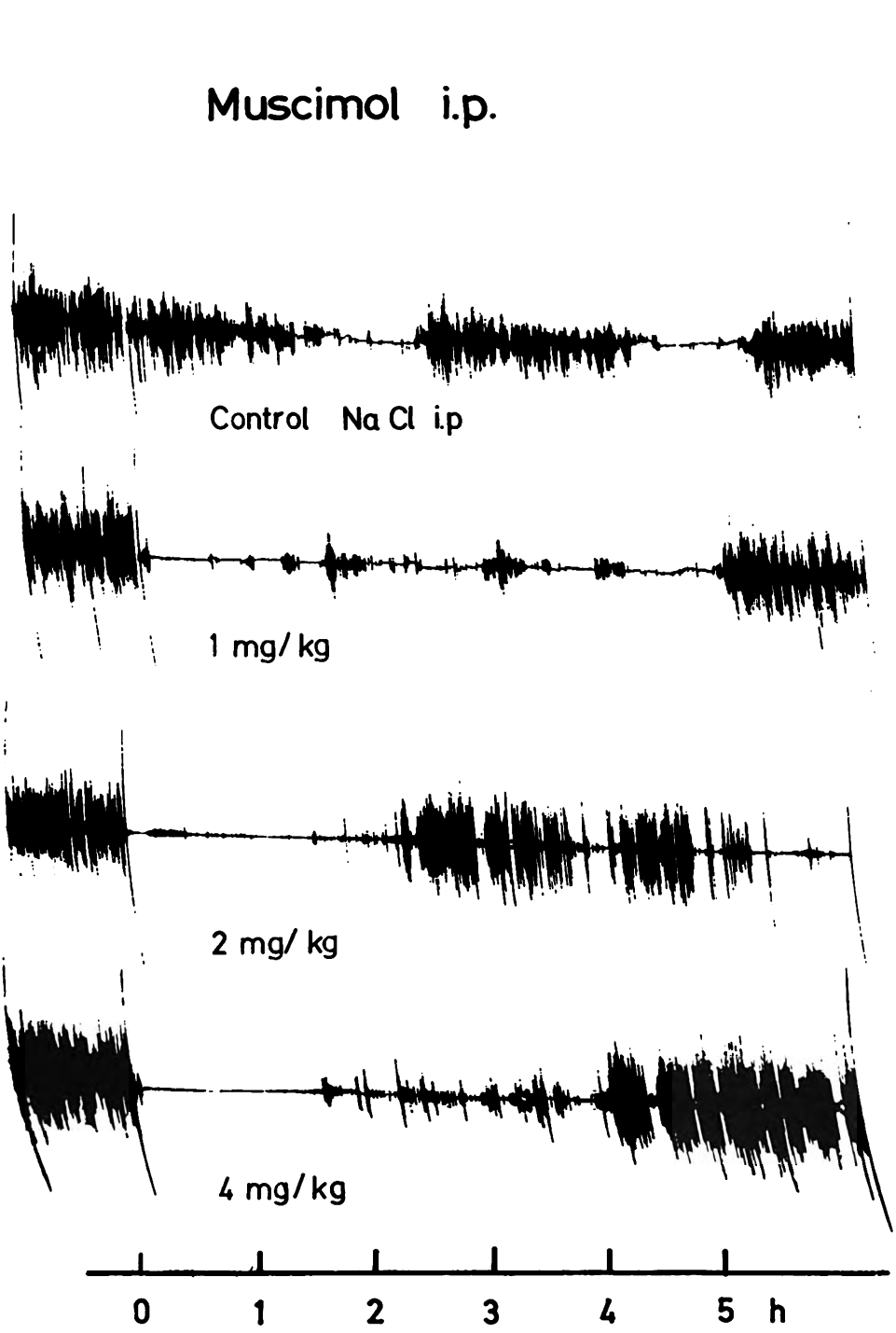

FIG. 6.—Muscimol sedates mice in jiggle cage with doses of 1, 2, and 4 mg/kg during 1–2 hours. Myoclonic cramps were recorded.

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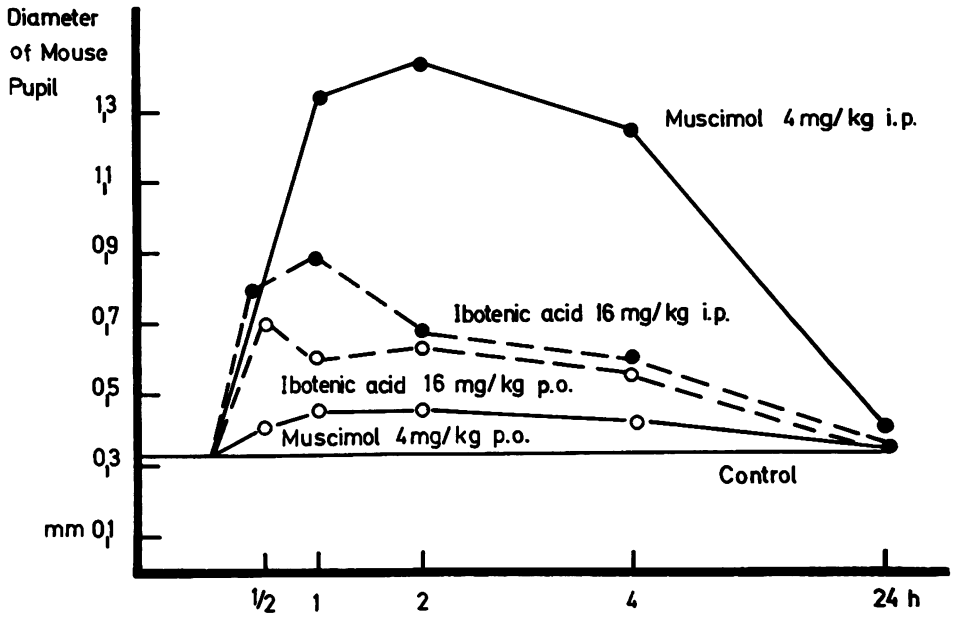

FIG. 7.—Dilatation of pupils by ibotenic acid and muscimol (groups of ten mice, statistical error not marked).

Another method we use is similar to the determination of antidepressant activity of neuro- and thymoleptics. It is based on the antagonism of reserpine-induced hypothermia. Liberation of catecholamines and serotonine in the brain makes mice sensitive to psychostimulating drugs (Askew, 1963). Mice are injected subcutaneously with 2 mg/kg reserpine and kept overnight at room temperature of 20° C. The rectal temperature is measured using a thermo-couple inserted to a depth of 2 cm. Groups of 8 mice are then injected intraperitoneally with the test drug or saline as control. CNS-stimulants (phenmetracine, amphetamine, methamphetamine, cocaine) and hallucinogenic drugs (LSD, Psilocybin), reverse the effect of reserpine and increase the rectal temperature within a few hours to normal values (Fig. 9, 10). The only exception is mescaline; it strongly depresses the temperature. Muscimol has an increasing effect on temperature like other hallucinogens, but only after 2–4 hours, whereas ibotenic acid keeps rectal temperature low (Fig. 11).

A third simple method to test psychotomimetic drugs is checking their effect on food intake. Hunger or appetite are the strongest drives in animal or man. They are easily influenced by central drug action. We have developed over the years different test methods to measure anorexogenic action (Spengler and Waser, 1957, 1959). Rats with a well controlled food intake are trained to a feeding period between 10 a.m. and 4 p.m. One hour before feeding time the test drug is injected intraperitoneally. At 12 a.m. and at the end of the feeding period (4 p.m.), the consumption of food is measured.

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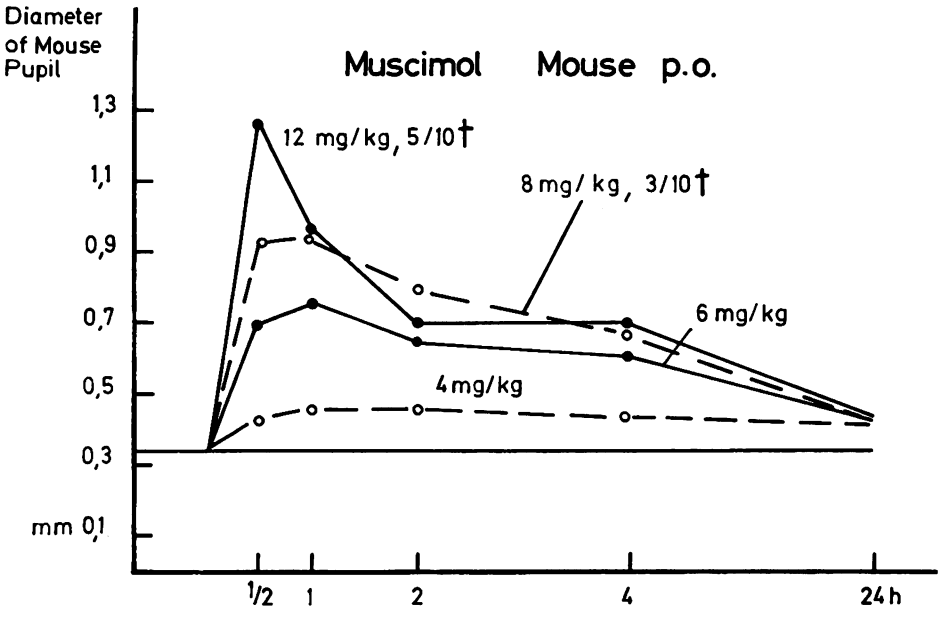

FIG. 8.—Action of muscimol per os on pupils of mice. Strong dilatations with toxic doses.

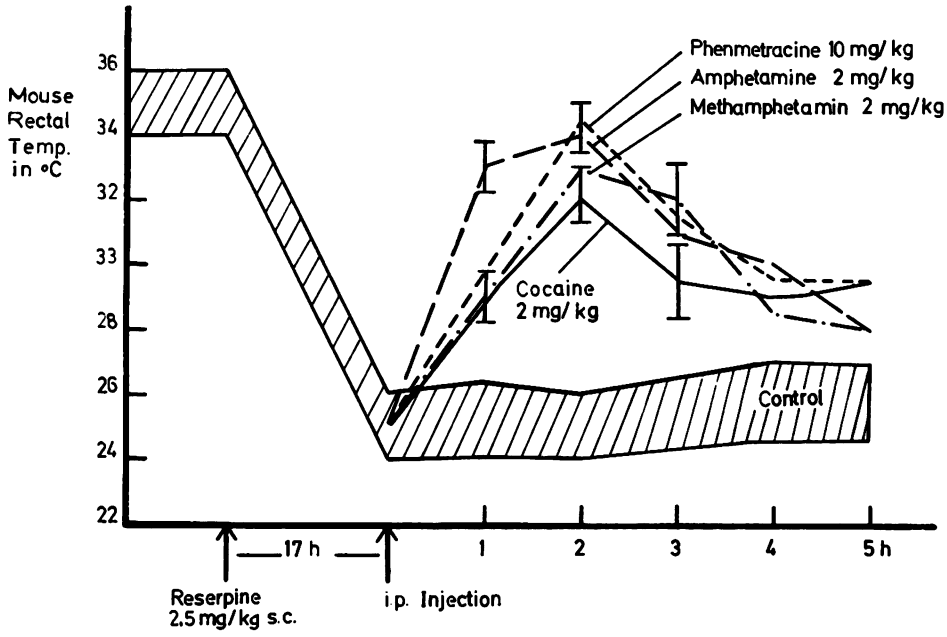

FIG. 9.—Rectal temperature of reserpinized mice (groups of 6 animals). Action of central stimulating drugs compared to control.

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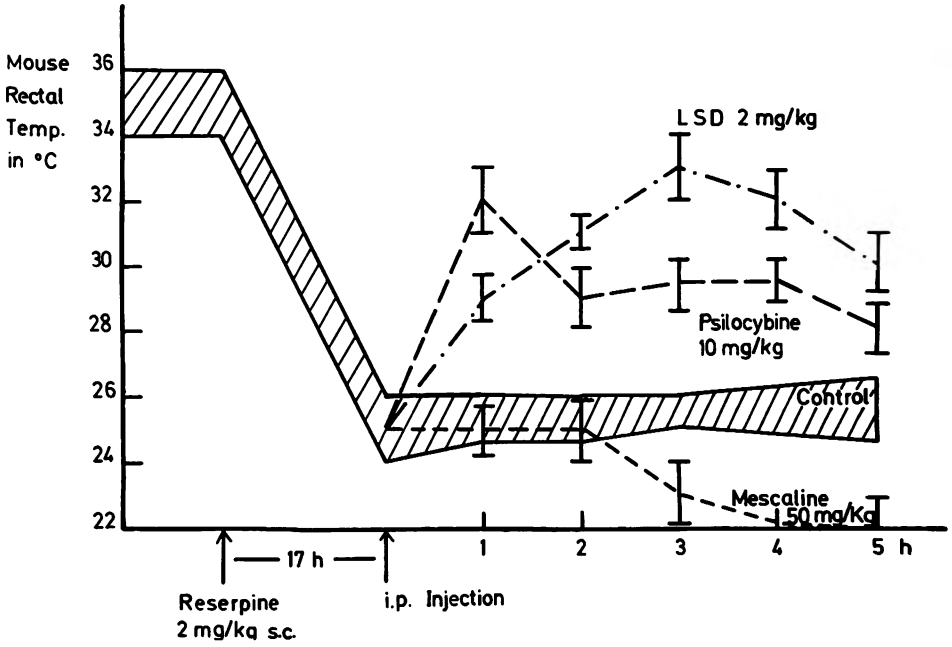

FIG. 10.—Rectal temperature of reserpinized mice under the influence of hallucinogenic drugs.

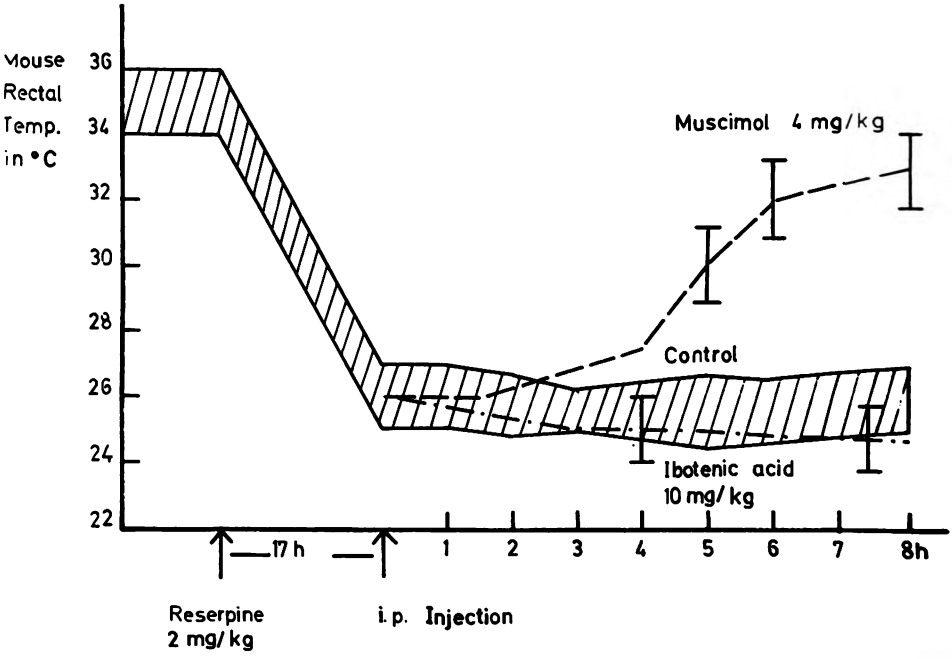

FIG. 11.—Rectal temperature of reserpinized mice under the influence of muscimol and ibotenic acid from Amanita muscaria.

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Most sympathomimetics and hallucinogens have a pronounced anorexogenic effect during some hours, probably by stimulating the satiety center in the hypothalamus (Waser and Spengler, 1963) (table 4). Muscimol and ibotenic acid act in a similar way in doses which are not hypnotic. After the experiment the rats may recover during two days with standardized feeding period before the next injections.

TABLE 4.—*Anorexogenic activity of drugs in diminishing normal food intake of rats to one half (ED 50)*

	mg/kg i.p.	Excitation
d-Amphetamine	2, 5	++
Ephedrine	17	+
Phenmetrazine	15	+
Methylphenidate	17	+
Scopolamine	0, 8	
Atropine	2, 5	+
Carbachol	1, 0	
Parpanit	35	
Mescaline	90	(+)
LSD	1	(+)
Psilocybin	18	+
Cocaine	30	+
Caffeine	250	+
Ibotenic acid	5, 0	
Muscimol	4, 0	

We have adapted this method to mice for a screening of small amounts of Amanita extracts. Mice are not as clean and trainable as rats, and we have not finally decided on the best technique. Using a special food container from which the fine grain cereal cannot be scattered and which remains tolerably clean, we are able to determine small differences in food intake. On mice the effects of muscimol and ibontenic acid are even stronger than the actions of LSD and amphetamine (Fig. 12, 13). We therefore think this kind of approach to be very promising for the screening of psychotropic compounds.

Central Nervous Effects In Man

Besides the well known descriptions of amanita-intoxication, not much is known about experiments with pure substances on man. Ibotenic acid and muscimol are now under careful investigation by a psychiatrist.[2] The work of the pharmacologist ends at this stage.

Curiosity is one of the main qualities of a scientist, and this may be the reason why a pharmacologist watching the behaviour of his animals under

[2] Prof. H. Heimann, Clinique psychiatrique universitaire Lausanne.

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certain drugs wants to know more about the emotions and changes in reaction they produce. Another reason is ethical. We have to foresee the accidents and dangerous actions new compounds of general interest may produce on man. My report on some experiments done on myself by ingesting ibotenic acid and muscimol under careful psychiatric control [3] may give you an unauthoritative view on this.

A 20 mg ibotenic acid dose ingested in water tastes like mushrooms, but produces little immediate action. Within half an hour a warm and slightly flushed face was noticed, without changes in blood pressure or heart rate with no psychic stimulation, but lassitude followed by sleep. One day later a migraine with classical one sided visual disturbance developed for the first time in my life. The occipitally localized headache continued in a milder form for two weeks.

Next I turned to muscimol. A dose of 5 mg in water orally ingested had little effect except a feeling of laziness. Ten mg produced a slight intoxication after 90 minutes with dizziness, ataxia and elevated mood, psychic stimulation (in psychological tests), no hallucinations but slight changes in taste and colour vision. Some myoclonic muscle twitching followed, then sleep with dreams. After two to three hours I felt normal, rested and able to undertake anything, even work. During the next night I slept well, deep and long. No other signs followed.

With 15 mg muscimol administered orally the intoxication started after 40 minutes and was more pronounced. Dizziness made walking with closed eyes impossible, but reflexes were not changed. Speech was sometimes inarticulate and dysarthric. Appetite and taste were diminished. After a phase of stimulation, concentration became more difficult. Vision was altered by endlessly repetitioned echo-pictures of situations a few minutes before. Hearing became noisy and sometimes was followed by echo. Most disturbing were repeated myoclonic cramps of different muscle groups. I felt sometimes as if I had lost my legs, but never had hallucinations as vivid and colourful as with LSD. The pupils remained always the same size. After 2 hours I fell asleep, but I cannot remember any dreams. Two hours later I awoke again and was glad that the muscle twitching was less frequent. I did not feel relaxed and fresh as after 10 mg. muscimol but rather dull and uncertain. Blood pressure was only a little elevated during the psychoactive phase. In preliminary experiments muscimol was detected in the urine by ion exchange separation and thin layer chromatography (C. H. Eugster).

Muscimol makes a toxic psychosis with confusions, dysarthria, disturbance of visual perception, illusions of colour vision, myoclonia, disorientation in situation and time, weariness, fatigue and sleep. Concentration tests show an improved performance with small doses (5 mg), but diminished performance and learning with an increased number of errors with higher doses (10–15 mg).

[3] PD Dr. J. Angst, Psychiatrische Universitätsklinik Zürich.

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Discussion

Different biologically active principles have been isolated from amanita muscaria. Some, as muscarine, acetylcholine, choline, ibotenic acid, muscimol and muscazon, were found by different scientists, but others were not confirmed by later research.

The action of muscarine is well known today, and it is generally accepted that muscarine is one of the most active parasympathomimetic drugs. This is partly due to its stability, as it is not hydrolized by cholinesterases. On the other hand, muscarine does not inhibit acetyl-cholinesterase in concentrations up to 10^{-4} m. It acts on the same receptors as acetylcholine, but its action is restricted predominantly to peripheral effector organs innervated by the autonomous nervous system. All cholinomimetic effects are antagonized by atropine.

Muscarine affects ganglionic synapses only by much higher doses than acetylcholine. With electrophoretic application on cortical Betz cells, muscarine shows an action 1–4 times as powerful as acetylcholine (Crawford and Curtis, 1966). But as we have seen, muscarine passes only with great difficulty through the intestinal wall, and the oral toxicity is remarkably low. The same must be said for the passage through the blood-brain barrier. Therefore, with the very low concentration of muscarine in the orally ingested mushroom, it is impossible that this alkaloid produces the psychotomimetic symptoms observed in amanita intoxication.

Acetylcholine and choline which are found in small, but varying amounts in the mushroom can as well not be held responsible for this action. Acetylcholine is immediately hydrolyzed by ubiquitous cholinesterases, and choline is practically inactive, especially when applied directly on central neurons.

The central action of amanita muscaria must be caused by the new aminoacids and amines detected in considerably high concentration in the mushroom. The described screening methods show especially for muscimol an intense central action, which is linked with the sympathetic system of the brain stem, as shown by the typical hyperthermic effects of reserpinized mice, central pupillary dilation and anorexia. Furthermore, the pyramidal and extrapyramidal motor systems are probably involved in some of the classical reactions as ataxia, catalepsy, convulsions and muscle twitches. But only with a further analysis may these symptoms be linked to specific sites of action as central ganglionic nuclei or spinal interneurons. The amines are considerably more active than the aminoacids, which are different with other centrally active catecholamines or tryptamines.

The most important finding surely is the psychotic action of muscimol as demonstrated in man. Although intense hallucinations as with LSD were missing with doses of 10–15 mg, there resulted considerable disturbance of psychic functions, such as orientation in situation and time, visual perception, process of thinking, speech, and some new psychic phenomena of illusions and perseveration of optical perception (echo pictures). Here again muscimol was more active than ibotenic acid, which showed only some unpleasant effects on the local circulation.

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When we compare now my personal psychotropic experiences with some descriptions of intoxications by amanita muscaria, we see in some respects an interesting parallelism. In the old literature (Donalies and Völz, 1960, Buck, 1963) and during this symposium (Brekhman and Sam, Wasson), the following symptoms were mentioned after ingestion of 1–4 mushrooms: dizziness, nausea, vertigo, somnolence, euphoria, sense of lightness, and coloured visions. Slight acoustic and optic hallucinations were noticed within the next few hours. A higher dose (5–10 mushrooms) produces severe effects of intoxication such as muscular twitching, leading to twitches of limbs; raving drunkenness with agitation and vivid hallucinations. Later, partial paralysis with sleep and dreams follow for many hours. Ingestion of more than 10 mushrooms is usually fatal. The hallucinogenic principle is excreted in the urine. It evokes the same symptoms when the urine is drunk again.

With 15 mg muscimol symptoms of the first group and muscular twitching were noticed. Hallucinations were not as vivid and colourful as expected. The picture would fit best for a dose of 5 mushrooms. As ibotenic acid produces only slight central action, probably muscimol is mainly responsible for these central effects. Further studies will show if muscimol is excreted unchanged and quantitatively in the urine. Other compounds in the mushroom may be responsible for its complex psychotic effect.

Summary

Because of its extraordinary pharmacological activity muscarine, the best known alkaloid of amanita muscaria, has been investigated for more than 100 years by chemists and pharmacologists. It was the first known drug with selective action on the autonomous nervous system. After its isolation in a pure and crystalline form (Eugster and Waser, 1954), its chemical structure and synthesis were established (Reviews by C. H. Eugster, S. Wilkinson). During the isolation process different screening methods were used. They are based on the strong parasympathomimetic activity of muscarine (Review by P. G. Waser, 1961). Until today nobody was able to show a direct psychotropic effect of muscarine on animal or man, probably due to its difficulty in passing the blood-brain barrier. In contrast, muscarine applied directly into the brain was shown to have an excitatory effect.

The active principles responsible for hallucinogenic or sedative symptoms described by different authors are only partly identified. Belladonna-like alkaloids, serotonin and bufotenin have not been extracted from the mushroom with certainty, but possibly there are other hydroxy-indoles present.

Lately Eugster, Theobald and colleagues (1965) discovered muscimol, ibotenic acid and muscazon in different varieties of amanita muscaria. These α-aminoacids and amine have pronounced sedative and hypnotic actions in mice, but little is known on their hallucinogenic activity. Their pharmacology on small animals was investigated with different methods. The temperature of reserpinized mice (2 mg/kg i.p.) is increased with orally 4 mg/kg

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muscimol as with LSD, psilocybin, amphetamine or cocaine, but not changed with 10 mg/kg ibotenic acid.

The diameter of mouse pupils is enlarged by intraperitoneal injection and oral ingestion of muscimol (4–8 mg/kg) and ibotenic acid (16 mg./kg). Both compounds showed a marked anorexogenic effect on mice (2–3 mg/kg oral) with sedation, hypnosis, muscle twitchings and catalepsy.

Most important is the psychotomimetic effect on man. Muscimol (10–15 mg oral dose) creates a toxic psychosis with confusions, dysarthria, disturbance of visional perception and hearing, illusions of colour vision, muscle twitching and myocloni, disorientation in situation and time, weariness, fatigue and sleep with dreams. Small doses (5 mg) improve performance in concentration tests, but large doses diminish psychic performances and learning. Ibotenic acid and muscazon have less central action. Muscimol is excreted in the urine.

Using different screening methods, we are now looking for other psychoactive principles in amanita muscaria.

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